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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,060	03/02/2004	Yoshihito Watanabe	118150	9829

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OLIFF & BERRIDGE, PLC
P.O. BOX 19928
ALEXANDRIA, VA 22320

EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,060	WATANABE ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) none is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/11/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-9 are pending.

The pending claims 1-9 are under examination in this Office action.

IDS

The reference cited in the IDS filed 5/11/04 has been considered by Examiner.

Specification/Claims Objection

The disclosure is objected to because of the following informalities:

On page 6, line 1, the article "a" before "64th amino acid residue" should be deleted. The same change should be made throughout the specification.

On page 9, "Figure 2 shows ..." should be changed to "Figure 2 (a-d) shows ...".

In claim 2, "and" before "an amino acid residue that forms a non-covalent bond to..." should be changed to "or".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recitation "a 64th amino acid residue of apomyoglobin" is indefinite because without setting forth sequence identifier (SEQ ID NO:_), the said residue 64 cannot be identified/determined. Note that amino acid sequences of myoglobin form which apomyoglobin is prepared vary from species to species, e.g., the myoglobin from Bos Taurus (cow) has 154 amino acid residues while the myoglobin from Sulculus diversicolor has 378 amino acid residues (see the attachments for "*NP 776306, myoglobin*" and "*CAA48412, myoglobin*", respectively).

Claim 8 is unclear in defining the groups: R^1, R^2, R^3 and R^4 in formula (1). Also, claim 8 is unclear in "*J represents ... hydrocarbons of 1 to 10 carbon atoms and two carbon atoms included in benzene rings*". The formula (1) represents a phosphino group containing compound wherein the J moiety covalently linked to the phosphino groups. How the J moiety can have the two carbon atoms participating in benzene rings? Clarification of this regard is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a metal complex-protein composite comprising (i) an apoprotein, e.g., apohemoglobin, apohemeoxygenase, apocatalase, apocytochrome and apoferritin, and (ii) a metal complex comprising rhodium or ruthenium or palladium metal ion, wherein the amino acid residue(s) of the said apoprotein coordinates to the metal ion thereof, and wherein the metal complex does not cause the apoprotein degradation or instability, e.g., Rh(I)(cod)(dppe)·BF4 (set forth in the specification, page 10), does not reasonably provide enablement for (A) the metal

complex-protein composite comprising variants of the apoprotein or the variants of a protein able to form a complex (non-covalent) with the metal ion thereof, and (B) any uncharacterized metal complex which has detrimental effect on the apoprotein to which the complex coordinates or bind. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

The current invention (claims 1-2 and the dependent claims thereto) is directed to a metal complex-protein composite comprising a protein able to form a complex with metal ion, e.g., rhodium, ruthenium and palladium. The specification does not teach amino acid sequence of said protein (e.g., apohemoglobin, apohemeoxygenase, apocatalase, apocytochrome and apoferritin). One skilled artisan thus cannot identify and characterize the cavity (pocket) that

interacts and/or hold the metal ion, nor make and use the variants of the protein so as to prepare the claimed metal complex-protein composite. Without knowing the amino acid sequence of the protein, one skilled in the art is unable to produce substitution mutation(s), e.g., substation of residue 64 (see claim 5). The specification does not provide working examples of the variant proteins which can coordinate to the above-mentioned metal ion. The specification does not teach or provide guidance as to selection and characterization of productive metal complex which does not destruct the protein to which the metal complex coordinates (see below).

(3) The unpredictability of the art:

In the absence of the amino acid sequence(s) for the protein or the apoprotein, the cavity of interacting with the metal ion cannot be determined, and producing the variant protein which has ability of forming a complex with (holding) the metal ion is unpredictable and requires undue experimentation. Not all mutations (e.g., substitution, deletion, insertion and truncation) in the protein, especially in or proximity to the metal in the cavity of the protein, result in productive apoprotein being capable of coordinating to the metal ion. It has been reported that substitution of residues 103 in human myoglobin protein has a destabilizing effect on the protein (see page 16542 of Witting et al. (2001) *J. Biol. Chem.* 276, 16540-16547). Note that residue 104 in myoglobin is in heme pocket (see Wagner et al. (1995) *J. Mol. Biol.* 247, 326-337). Hence, the mutagenesis of the protein, e.g., hemoglobin, hemeoxygenase, catalase, cytochrome and ferritin would give rise to a large quantity of mutants; of them, there must be nonproductive/inactive apoproteins of said proteins which are defective in binding with the metal ions. Therefore, the skilled artisan is required to conduct undue experimentation to scan and characterize active apoprotein capable of coordinating to the metal ions thereof.

Not any metal complexes formed by the claimed metal ion, i.e., rhodium or ruthenium or palladium are productive. Zhu et al. (*J. Am. Soc.* (1994) 116, 5218-5224) have shown that some palladium (II) (Pd II) complexes cleave apocytochrome (see abstract, pages 5222, the left column). Identifying the metal complexes thus is unpredictable; and therefor, screening for and characterizing the metal ions which at least do not have degradative effect on the corresponding apoproteins claimed in this application require undue experimentation.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify the variants (mutated apoprotein) which retain ability of binding the above-mentioned metal ion(s), the specification needs to provide sufficient guidance to be considered enabling.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing numerous variants resulted from the mutagenesis (deletion, substitution, inserting and truncation).

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the

preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in metalloorganic chemistry, peptide chemistry, organic synthesis and protein engineering as well as knowledge in molecular biology, and biochemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An undue level of skill is needed for the skilled artisan in order to make and characterize the metal complex-protein composite wherein the protein is the variant produced by mutagenesis.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Jackson et al. (Book of Abstract (2000) 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000, Abstract No. 510).

Jackson et al. teach a metal complex protein composite comprising cytochrome protein complexed with ruthenium (Ru), wherein Ru is prepared as a metal complex, e.g., *trans*-$[Ru(bpy)_2(OH_2)_2](CF_3SO_3)_2$, which anticipates instant claim 1.

Jackson et al. teach that histidine residues of said protein coordinate to the metal complex, which anticipates instant claim 2.

Also, Jackson et al. teach apocytochrome protein which is heme-free in said composite, which anticipates instant claims 3-4.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson et al. (Book of Abstract (2000) 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000, Abstract No. 510) taken with Smolenski et al. (*Inorg. Chem.* (2003, March) 42, 3318-3322) and Cadierno (*Inorg. Chem.* (2003, May) 42, 3293-3307).

The teachings of Jackson et al. applied to the instant claims 1-4 have been discussed above.

Yet, Jackson et al. do not expressly teach that the composite comprises the Ru metal complex that has a phosphino group.

Smolenski et al. teach a water-soluble phosphino complexes of ruthenium (Ru), which meets the limitations with respect to the phosphino moieties, as applied to instant claims 6 and 8.

The Cadierno et al. teach that the phosphino group is a diphenylphosphino derivative (see abstract, and pages 3295, scheme 1 and Table 2), as applied to instant claims 6 and 7. Since the Cadierno's complexes read on the claim 8 Formula I, the above Cadieno's teaching is applied to instant claim 8.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the ligand compound of $Ru(bpy)_2$ (wherein)which coordinates to the Jackson's Ru metal ion for the Smolenski et al. phosphino ligand compound, or for the Cadierno et al. ligand compound comprising diphenylphosphino groups because the following reasons.

The Smolenski's complexes 2 and 3 of the Ru metal complex of comprising phosphino groups have high selectivity of hydrogenating C=O bond (see abstract and page 3321, the right column in).

The Smolenski's phosphino compound (e.g., trialkylphosphines) is hydrophilic (see page 3322) suitable for engineering into amino acid environment of a protein.

The Cadierno's Ru-diphenylphosphino complex is easily prepared *via* a single chemical reaction with excellent yield (see page 3307).

Further, the Cadierno's diphenylphosphino derivative (ligands that coordinates to the Ru metal ion) offers advantages of a versatile coordination ability in ruthenium fragments (e.g., Ru(II) and Ru(IV)).

Therefore, it would have been *prima facie* obvious to prepare the above-mentioned metal complex-protein composite wherein the Ru metal complex has structural feature of the instant formula 1 and wherein ligand in said complex is a phosphino derivative, e.g., diphenylphosphino groups.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel W. Liu, Ph.D.
September 28, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER